ELITE-2 study

Cox Proportional Hazard Analysis of the impact of being on spironolactone/aldactone at baseline (BL) on the subsequent development of weight gain >5%. The impact is highly significant (p<0.0001) and independent of the severity of heart failure as measured by LVEF, NYHA class, clinical oedema status, degree of kidney dysfunction (i.e. creatinine [crea] levels) and heart failure aetiology. The impact of spironolactone therapy is also independent of other parameters, including cholesterol levels (chol) and uric acid levels (UA). In 3030 patients all information for this analysis was available.

Survival Summary Table for FU days gain 5%
Censor Variable: gain5% y=0/no=1
Model: Proportional Hazards
Row exclusion: ELITE2_11-05B-w-change-080805

# Obs.	3030
# Events	846
# Censored	2184
% Censored	72.079
# Missing	98
# Invalid	0

Model Coefficients for FU days gain 5%
Censor Variable: gain5% y=0/no=1
Model: Proportional Hazards
Row exclusion: ELITE2_11-05B-w-change-080805

was_on_spiro_/_aldacto_d1: Spiro yes
DRUG AL/BC: A
Sex: FEMALE
LVEF (%)
BEST NYHA
BL UA
BL creat
was_on_BB: BB yes
CHOL BL value
Aetiology_short: Isch
Edema status at baseline: full edema vs trace vs no edema
  no edema
  trace edema
Age

DF	Coef	Std. Error	Coef/SE	Chi-Square	P-Value	Exp(Coef)
1	.670	.105	6.408	29.242	<.0001	1.788
1	.282	.069	4.072	16.582	<.0001	1.326
1	.101	.079	1.273	1.620	.2031	1.106
1	-.016	.005	-3.166	10.023	.0015	.984
1	.124	.063	1.985	3.941	.0471	1.132
1	.001	3.118E-4	3.944	16.555	<.0001	1.001
1	-1.256E-4	.001	-.096	.009	.9235	1.000
1	-.095	.088	-1.089	1.186	.2762	.909
1	-.027	.029	-.925	.855	.3551	.973
1	-.184	.077	-2.387	5.699	.0170	.832
2	.	.	.	8.765	.0125	.
1	.183	.101	1.815	3.296	.0695	1.201
1	-.064	.121	-.530	.281	.5964	.938
1	-.010	.005	-1.939	3.761	.0525	.990

ELITE-2 study
Cox Proportional Hazard Analysis.
Below are the individual hazard ratios and their 95% confidence interval related to the analysis on page 1.

Confidence Intervals for FU days gain 5%
Censor Variable: gain5% y=0/no=1
Model: Proportional Hazards
Row exclusion: ELITE2 11-05B-w-change-080805

	Exp(Coef)	95% Lower	95% Upper
was_on_spiro_/_aldaclo_d1: Spiro yes	1.768	1.438	2.174
DRUG AL/BC: A	1.326	1.158	1.519
Sex: FEMALE	1.106	.947	1.291
LVEF (%)	.984	.975	.994
BL NYHA	1.132	1.002	1.280
BL UA	1.001	1.001	1.002
BL creat	1.000	.897	1.002
was_on_BB: BB yes	.909	.765	1.079
CHOL BL value-	.973	.919	1.031
Aetiology_short: Isch	.832	.715	.968
Edema status at baseline: full edema vs trace vs no edema : none	1.201	.986	1.465
Edema status at baseline: full edema vs trace vs no edema: trace	.938	.741	1.188
Age	.990	.980	1.000

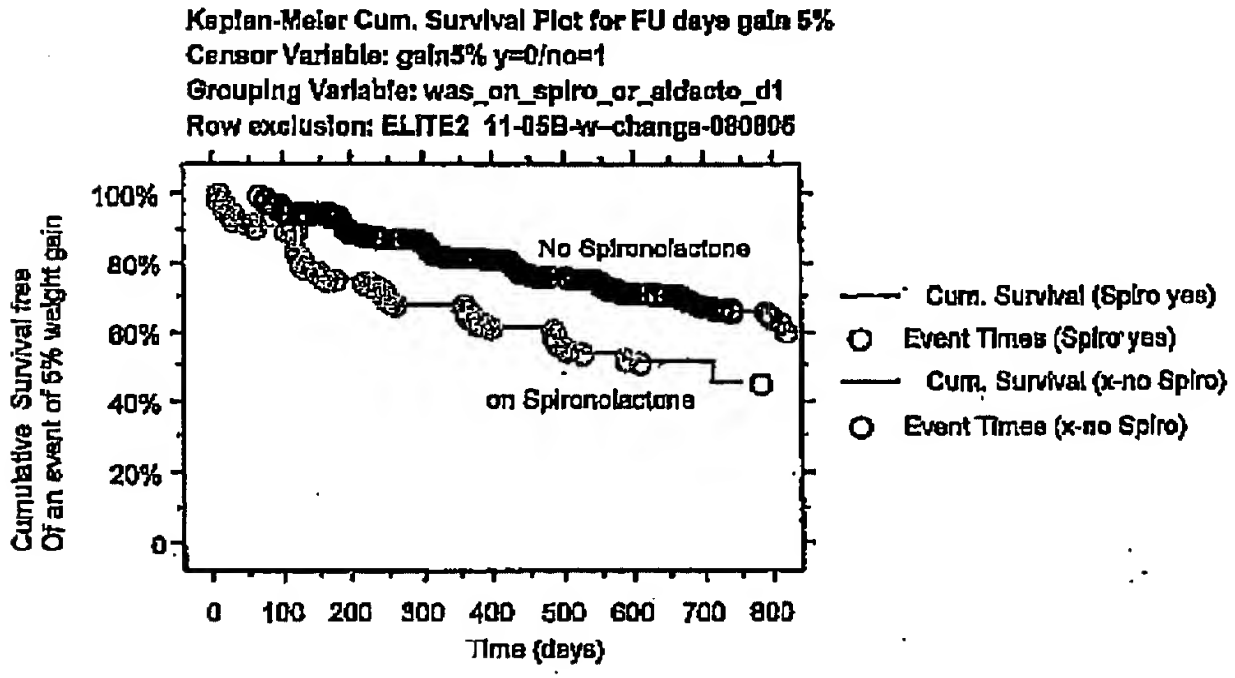
ELITE-2 study
Kaplan-Meier Analysis of the impact of being on spironolactone/aldactone at baseline on the subsequent development of weight gain >5%. The impact is highly significant (p<0.0001).
The graph shows, that patients with spironolactone are more likely to gain weight.

Survival Summary Table for FU days gain 5%
Censor Variable: gain5% y=0/no=1
Grouping Variable: was_on_spiro_or_aldacto_d1
Row exclusion: ELITE2 11-05B-w-change-080805

	# Obs.	# Events	# Censored	% Censored	# Missing	# Invalid
Spiro yes	264	108	156	59.091	0	0
x-no Spiro	2864	773	2091	73.010	0	0
Total	3128	881	2247	71.835	0	0

Rank Tests for FU days gain 5%
Censor Variable: gain5% y=0/no=1
Grouping Variable: was_on_spiro_or_aldacto_d1
Row exclusion: ELITE2 11-05B-w-change-080805

	Chi-Square	DF	P-Value
Logrank (Mantel-Cox)	36.260	1	<.0001
Breslow-Gehan-Wilcoxon	37.003	1	<.0001
Tarone-Ware	36.699	1	<.0001
Peto-Peto-Wilcoxon	36.643	1	<.0001
Harrington-Fleming (rho = .5)	36.120	1	<.0001



Cox Proportional Hazard Analysis of the impact of being on spironolactone/aldactone or statin at baseline on the subsequent development of weight gain >5%. The analysis shows an important trend for a 53.1% increase in the occurrence of >5% weight gain when a patient was on spironolactone. Treatment with a beta blocker (which is not indicated in patients with COPD) was associated with a 7.5% increase in the occurrence of >5% weight gain.

These results are independent of the severity of heart failure as measured by LVEF, NYHA class, clinical oedema status, and the degree of kidney dysfunction (i.e. creatinine [crea] levels). This analysis was performed on 259 patients with COPD – in 60 of these patients a weight gain >5% event occurred.

Importantly, this analysis shows that good cardiac function (e.g. high LVEF) was not related to experiencing weight gain. In fact, per % increase in LVEF a 2.1% decrease in the frequency of >5% weight gain was observed, and

Survival Summary Table for FU days gain 5%
Censor Variable: gain5% y=0/no=1
Model: Proportional Hazards
Row exclusion: ELITE2 11-05B-w-ch-COPD-080805

# Obs.	259
# Events	60
# Censored	199
% Censored	76.834
# Missing	0
# Invalid	1

Model Coefficients for FU days gain 5%
Censor Variable: gain5% y=0/no=1
Model: Proportional Hazards
Row exclusion: ELITE2 11-05B-w-ch-COPD-080805

	DF	Coef	Std. Error	Coef/SE	Chi-Square	P-Value	Exp(Coef)
was_on_spiro_/_aldacto_d1: Spiro yes	1	.432	.395	1.094	1.198	.2737	1.541
LVEF (%)	1	-.021	.021	-1.013	1.027	.3109	.979
was_on_BB: BB yes	1	.089	.337	.264	.070	.7916	1.093
BL creat	1	-.008	.006	-1.424	2.027	.1546	.992
BL NYHA	1	-.024	.212	-.112	.012	.9111	.977

ELITE-2 study - the subgroup of patients with a diagnosis of COPD.
Cox Proportional Hazard Analysis.
Below are the individual hazard ratios and their 95% confidence interval related to the analysis on page 4.

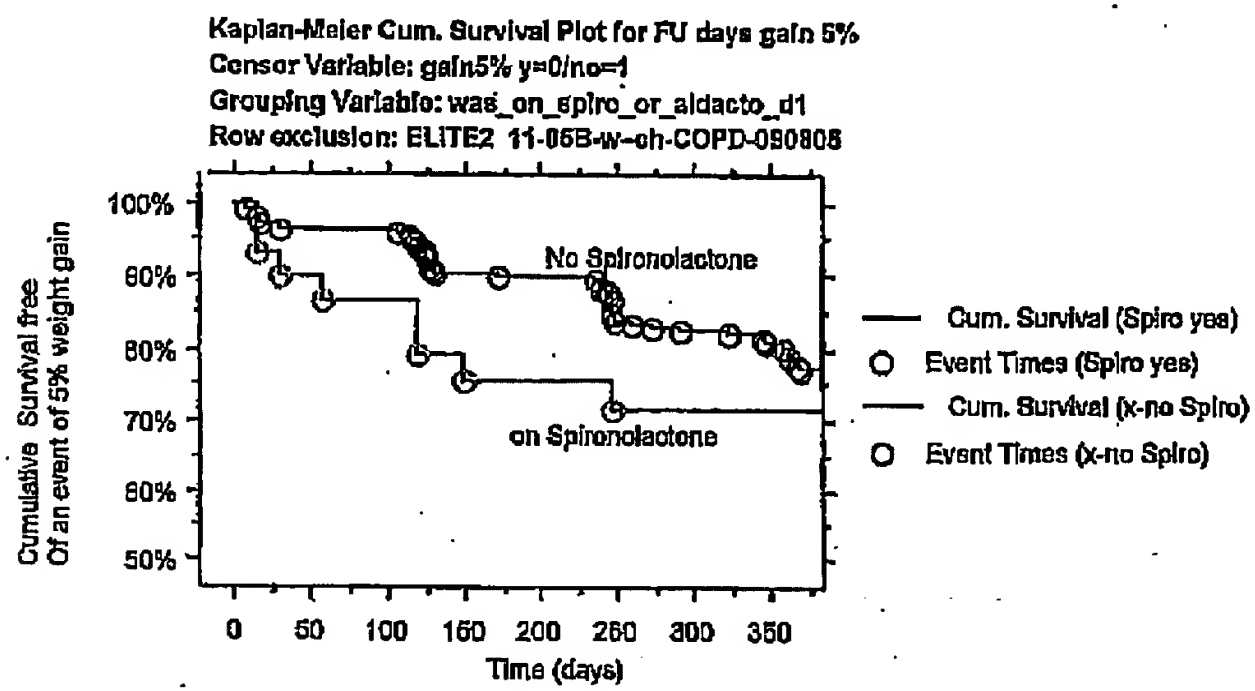
Confidence Intervals for FU days gain 5%
Censor Variable: gain5% y=0/no=1
Model: Proportional Hazards
Row exclusion: ELITE2 11-05B-w-oh-COPD-090805

	Exp(Coef)	95% Lower	95% Upper
was_on_spiro_/_aldacto_d1: Spiro yes	1.541	.710	3.344
LVEF (%)	.979	.940	1.020
was_on_BB: BB yes	1.093	.564	2.118
BL creat	.992	.981	1.003
BL NYHA	.877	.644	1.480

ELITE-2 study - the subgroup of patients with a diagnosis of COPD.

Kaplan-Meier Analysis of the impact of being on spironolactone/aldactone at baseline on the subsequent development of weight gain >5%in 12 months of follow-up.

The graph shows, that patients with spironolactone are more likely to gain weight.



ELITE-2 study - the subgroup of patients with a diagnosis of COPD.

Cox Proportional Hazard Analysis of the impact of being on a beta blocker or on spironolactone/aldactone at baseline (BL) on the subsequent development of weight loss >6%. The analysis shows a strong trend for a 55.3% decrease in the occurrence of >6% weight loss when a patient was on a beta blocker (p=0.088) and a 36.4% decrease in the occurrence of >6% weight loss when a patient was on spironolactone.

Treatment with a beta blocker (which is typically contraindicated for patients with COPD) or spironolactone (which in heart failure has the effect of a diuretic and should result in weight loss) was associated with less weight loss independently of the severity of heart failure as measured by LVEF, NYHA class and the degree of kidney dysfunction (i.e. creatinine [crea] levels). This analysis was performed on 259 patients with COPD – in 55 of these patients a weight loss >6% event occurred.

Importantly this analysis shows that good cardiac function (e.g. high LVEF) was not related to prevention of weight loss. In fact per % increase in LVEF a 1% increase in the frequency of >6% weight loss was observed.

Survival Summary Table for FU days w.loss 6%
Censor Variable: w.loss 6% y=0/no=1
Model: Proportional Hazards
Row exclusion: ELITE2 11-05B-w-ch-COPD-090805

# Obs.	259
# Events	55
# Censored	204
% Censored	78.764
# Missing	0
# Invalid	1

Model Coefficients for FU days w.loss 6%
Censor Variable: w.loss 6% y=0/no=1
Model: Proportional Hazards
Row exclusion: ELITE2 11-05B-w-ch-COPD-090805

	DF	Coef	Std. Error	Coef/SE	Chi-Square	P-Value	Exp(Coef)
was_on_BB: BB yes	1	-.806	.472	-1.707	2.915	.0878	.447
LVEF (%)	1	.012	.023	.516	.266	.6068	1.012
BL NYHA	1	.335	.215	1.555	2.418	.1200	1.397
BL creatinine	1	-.002	.006	-.414	.171	.6792	.998
was_on_spiro_/_aldacto_d1: Spiro yes	1	-.453	.486	-.933	.871	.3506	.636

ELITE-2 study - the subgroup of patients with a diagnosis of COPD.

Cox Proportional Hazard Analysis.
Below are the individual hazard ratios and their 95% confidence interval related to the analysis on page 7.

Confidence Intervals for FU days w.loss 6%
Censor Variable: w.loss 6% y=0/no=1
Model: Proportional Hazards
Row exclusion: ELITE2 11-05B-w-ch-COPD-080805

	Exp(Coef)	95% Lower	95% Upper
was_on_BB: BB yes	.447	.177	1.127
LVEF (%)	1.012	.967	1.059
BL NYHA	1.397	.916	2.131
BL creatinine	.998	.986	1.009
was_on_spiro_/_aldacto_d1: Spiro yes	.638	.246	1.645

ELITE-2 study - the subgroup of patients with a diagnosis of COPD.

Kaplan-Meier Analysis of the impact of being on a beta blocker at baseline on the subsequent development of weight loss >6% during follow-up, particularly after >200 days of follow-up.

The graph shows, that COPD patients in the ELITE 2 trial treated with a beta blocker are less likely to suffer weight loss. The log-rank p-value for this observation is 0.082.

Survival Summary Table for FU days w.loss 6%
Censor Variable: w.loss 6% y=0/no=1
Grouping Variable: was_on_BB_not_timolol_d1
Row exclusion: ELITE2 11-05B-w-ch-COPD-090805

	# Obs.	# Events	# Censored	% Censored	# Missing	# Invalid
BB yes	44	5	39	88.636	0	0
no BB	215	50	165	76.744	0	1
Total	259	55	204	78.764	0	1

Rank Tests for FU days w.loss 6%
Censor Variable: w.loss 6% y=0/no=1
Grouping Variable: was_on_BB_not_timolol_d1
Row exclusion: ELITE2 11-05B-w-ch-COPD-090805

	Chi-Square	DF	P-Value
Logrank (Mantel-Cox)	3.026	1	.0820
Breslow-Gehan-Wilcoxon	1.921	1	.1658
Tarone-Ware	2.384	1	.1218
Peto-Peto-Wilcoxon	2.803	1	.0941
Harrington-Fleming (rho = .5)	2.918	1	.0876